REMARKS

Claims 1-20 are pending in this application. Claims 2, 4, 8, 9, and 12-20 have been withdrawn as being directed to a non-elected invention. The disclosure is objected to for incorrectly referencing a PCT application. Claim 11 is objected to for failing to further limit the subject matter of a preceding claim. Claims 3, 5, 7, 10, and 11 are rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. Claim 5 is rejected under 35 U.S.C. § 112, second paragraph, for lack of clarity. Claims 1, 3, 5-7, 10 and 11 are rejected under 35 U.S.C. § 103(a) for obviousness over Deboer (U.S. Patent No. 5,633,076; hereinafter "Deboer"), Clark (U.S. Patent No. 5,32,775; hereinafter "Clark"), or Lubon (U.S. Patent No. 5,831,141; hereinafter "Lubon") in view of Morinaga et al. (PNAS 80:4604-4608; 1983; hereinafter "Morinaga") and Bennett (Breast Cancer Res. Treatment 45:169-179, 1997; hereinafter "Bennett"). By this reply, Applicants amend claims 3, 5, 7, 10, and 11, and address each of the Examiner's rejections.

Support for the Amendment

Support for the amendment to claims 3, 7, and 10 is found in the specification on, e.g., page 6, lines 7-8, and page 8, lines 14-18. Support for the term "non-human transgenic mammal" in claim 10 is found in, e.g., claim 3. Support for the amendment to claim 11 is found on, e.g., page 15, line 17, through page 16, line 1, of the specification. Claim 5 has been amended to correct the claim dependency. No new matter is added by the amendment.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 3, 5, 7, 10, and 11 are rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. The Examiner states that

> the specification, while being enabling for a non-human transgenic mammal whose genome comprises a transgene that results in expression of rHuAFP in mammary epithelial cells, does not reasonably provide enablement for a chimeric mammal wherein only a variable portion of the cells of the animal comprises a transgene that results in expression of rHuAFP in the mammary epithelial cells wherein the rHuAFP is secreted into the milk of the mammal. (Office Action, p.3.)

Applicants have amended independent claims 3, 7, and 10 to recite that the *genome* of the

mammal comprises a transgene that results in the expression of rHuAFP in mammary epithelial cells. Because the scope of present claims 3, 7, 10, and 11, and claims dependent therefrom, has been deemed enabled by the Examiner, Applicants respectfully request that the rejection of claims 3, 5, 7, 10, and 11 be withdrawn.

Claims 10 and 11 are further rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. The Examiner states that the specification is enabling "for a method of producing a rHuAFP that is secreted in the milk of a transgenic mouse wherein the mouse is made by introducing the transgene into cells of an embryo or into mouse ES cells," but the specification "does not reasonably provide enablement for any such mammal made using any cell type or a transgenic human made using any method" (Office Action, pp. 5-6). Applicants have amended claim 10 to recite a method of producing rHuAFP that is secreted into the milk of a *non-human transgenic mammal*. Because claims 10 and 11 no longer encompass the production of transgenic humans that secrete rHuAFP into their milk, this aspect of the rejection of claims 10 and 11 can now be withdrawn. Applicants respectfully disagree that the specification does not reasonably enable the method of present claims 10 and 11, which is not limited by the type of transgenic non-human mammal made or the cell type used to make the transgenic non-human mammal.

As evidence that the invention recited in present claims 10 and 11 is enabled, Applicants provide a Declaration of Edward J. Stewart, who is the Director of Business Development at Merrimack Pharmaceuticals, Inc., the exclusive licensee of the present application.[1] In paragraph 4 of the Declaration, Mr. Stewart states that he interacted with the inventors, and the scientists who were working under the direction of the inventors, and that the scientists used methods disclosed in the specification and known in the art to successfully produce several transgenic mice and goats capable of expressing rHuAFP and secreting it into their milk.

For example, paragraphs 5, 6, and 7 of the Declaration state that several transgenic mice were generated by microinjecting the rHuAFP transgene into male pronuclei, which were used to fertilize female ova. The resulting microinjected embryo was then implanted into the oviduct of a pseudo-pregnant recipient female mouse. This method is taught on page 13, lines 10-15, of the

1 Applicants note that the Declaration is provided unsigned; a signed copy will be provided.

specification.

Paragraphs 5, 6, and 7 of the Declaration also state that several transgenic goats were generated by transfecting somatic cells with the rHuAFP transgene and using nuclear transfer methods to transfer the nuclei of a transfected somatic cell to an enucleated oocyte. This method, which was referenced in Applicants' specification (see, e.g., page 14, lines 4-8), was known in the art prior to Applicants' filing date and involved surgically collecting oocytes, enucleating the oocytes, and reconstructing the oocytes with an individually isolated transfected somatic cell (karyoplast). Once reconstructed, the couplet (enucleated oocyte and somatic cell) were fused together by an electrical pulse which simultaneously activated the reconstructed embryo. The activated embryo was then placed into culture for 24-48 hours and then transferred to a suitable recipient animal (see again paragraph 5 of the Declaration). Seventeen transgenic goats expressing rHuAFP have been produced using this method, which is taught by the present specification (see paragraph 7 of the Declaration).

Exhibit A is a photograph of "Merri," a transgenic founder goat expressing rHuAFP in its milk, which was made according to the methods disclosed in the specification. Exhibit B is a photograph confirming that the genotype of the transgenic founder goat, Merri, now includes the rHuAFP transgene, which has been amplified by PCR, based on its presence in blood and ear tissue. Exhibit C is a photograph of a Southern blot demonstrating that Merri contains two copies of the HuAFP transgene in a diploid genome, thereby ruling out any gross transgene rearrangement. Finally, Exhibit D is a photograph showing that the HuAFP transgene integrated at a single site on the "q" terminal end on a mid to large sized autosomal chromosome, as determined by fluorescent *in situ* hybridization (FISH). As is apparent from the enclosed Exhibits A-D, the methods disclosed in the specification and known in the art can be successfully used to produce transgenic animals capable of expressing rHuAFP and secreting it into their milk.

The evidence provided in the Declaration of Edward J. Stewart clearly demonstrates that transgenic mammals expressing and secreting rHuAFP in their milk can be and, in fact, were successfully produced using the methods taught in the present specification. Accordingly, one skilled in the art can successfully practice the full scope of present claims 10 and 11 using the

guidance provided in the instant specification and the knowledge generally available in the art. For this reason, Applicants respectfully request that the rejection of claims 10 and 11 under 35 U.S.C. § 112, first paragraph, be withdrawn.

Rejections under 35 U.S.C. § 112, second paragraph

Claim 5 is rejected under 35 U.S.C. § 112, second paragraph, for indefiniteness for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner states that claim 5, which is drawn to the non-human transgenic mammal of claim 1 or 2, lacks antecedent basis because "claims 1 and 2 are both drawn to nucleic acids, not non-human transgenic mammals" (Office Action, p. 10). Applicants have amended claim 5 so that it now depends from claim 3, which is directed to a non-human transgenic mammal. Accordingly, the rejection of claim 5 can now be withdrawn.

Rejections under 35 U.S.C. § 103

Claims 1, 3, 5-7, 10, and 11 are rejected under 35 U.S.C. § 103(a) for obviousness over Deboer, Clark, or Lubon in view of Morinaga and Bennett. The Examiner states:

> Deboer taught generating transgenic cows and mice using transgenes encoding human serum albumin..., human lactoferrin...or human lysozyme...operably linked to the αS1 casein promoter...or β lactoglobulin promoter...and a signal sequence...by microinjecting transgene constructs into the pronuclei of fertilized oocytes or into the nuclei of each of a 2-cell embryo...which are cells as required by claim 10. The embryos were grown to generate mammals who later express the recombinant protein in the milk. (Office Action, p. 11.)

Applicants respectfully traverse the rejection of claims 1, 3, 5-7, 10, and 11.

To reject a claim under 35 U.S.C. § 103(a), the Patent Office bears the initial burden of showing an invention to be *prima facie* obvious over the prior art. *See In re Bell*, 26 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1993). Three basic criteria must be met to establish a *prima facie* case of obviousness. First, the prior art must teach or suggest all of the claim limitations. *In re Wilson*, 165 U.S.P.Q. 494, 496 (CCPA 1970). Second, the prior art must provide "motivation, suggestion, or teaching of the desirability of making the specific combination that was made by

the applicant." *See In re Kotzab*, 55 U.S.P.Q.2d 1313, 1316 (Fed. Cir. 2000). Third, the cited references must provide a reasonable expectation of successfully achieving the claimed invention. *In re Vaeck*, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). Applicants respectfully submit that *prima facie* obviousness has not been established: the Examiner has not pointed out anything in the prior art that could reasonably be viewed as a suggestion, teaching, or motivation to modify or combine the cited references to arrive at the claimed invention. "Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability – the essence of hindsight." *In re Dembiczak*, 50 U.S.P.Q.2d 1614, 1617 (Fed. Cir. 1999).

Present independent claim 1 is directed to a substantially pure nucleic acid molecule encoding rHuAFP under the control of a milk-specific promoter, and having a leader sequence that enables secretion of rHuAFP by milk-producing cells into the milk of a mammal (i.e., a rHuAFP transgene). Present independent claim 3 is directed to a non-human transgenic mammal in which the genome of every cell of the mammal contains a rHuAFP transgene that promotes the expression of rHuAFP by mammary epithelial cells of the mammal so that the rHuAFP is secreted into the mammal's milk. Present claim 5 depends from claim 3. Present independent claim 6 is directed to the milk of a non-human mammal that contains rHuAFP. Present claim 7 depends from claim 6. Finally, present independent claim 10 is directed to a method of producing rHuAFP that is secreted into the milk of a non-human transgenic mammal by providing a cell transfected with a rHuAFP transgene, growing the transfected cell to produce a non-human transgenic mammal whose genome contains the transgene, in which the transgene promotes rHuAFP expression by mammary epithelial cells of the mammal and its secretion into the milk of the mammal, and collecting the milk containing the rHuAFP from the mammal. Present claim 11 depends from claim 10. Applicants will first characterize each individual reference cited, distinguishing them individually over present claims 1, 3, 5-7, 10, and 11, and then provide reasons for why the *combination* of cited reference does not establish a *prima facie* case of obviousness against claims 1, 3, 5-7, 10, and 11.

Deboer discloses a method of producing transgenic non-human animals (i.e., non-human primates, mice, cattle, dogs, pigs, and sheep) that produce recombinant polypeptides (i.e.,

exogenous proteins: human milk proteins, such as lactoferrin, lysozyme, secreted immunoglobulins, lactalbumin, bile salt-stimulated lipase, human serum proteins, such as albumin, immunoglobulins, Factor VIII, Factor IX, protein C, and industrial enzymes, such as proteases, lipases, chitinases, and liginases, and endogenous proteins: bovine milk proteins, such as αS1, αS2, β- and κ-casein, β-lactoglobulin lactoferrin, lysozyme, cholesterol hydrolase, serum proteins, such as serum albumin, and proteinaceous hormones, such as growth hormones) in the milk of the female transgenic animals (see, e.g., col. 6, line 40, through col. 7, line 35). Deboer exemplifies the production of recombinant polypeptides in transgenic cows and mice. Deboer, despite listing many proteins to be expressed in the described system, fails to make mention of rHuAFP.

Clark discloses a method of producing a recombinant polypeptide (i.e., peptide hormones, blood coagulation factors (e.g., factors VIII and IX or subunits thereof, blood proteins, e.g., beta-globin, and serum proteins, e.g., alpha$_1$-antitrypsin) proteins for foodstuffs, including natural or altered milk proteins of the host mammal, or enzymes) in the milk of a transgenic non-human mammal (i.e., mice, sheep, goats, pigs, and cattle; see, e.g., col. 1, line 39, through col. 2, line 11, col. 3, lines 58-66, and col. 18, line 25, through col. 19, line 11). Clark exemplifies the production of recombinant alpha$_1$-antitrypsin and Factor XI in transgenic sheep and recombinant beta lactoglobulin in mice. Clark also fails to mention rHuAFP.

Lubon discloses the production of recombinant human protein C in the milk of a transgenic animal (i.e., a mouse, a rat, a rabbit, a pig, a sheep, a goat, or a cow; see, e.g., col. 3, line 39, through col. 5, line 55, and col. 7, lines 34-38). Lubon exemplifies the production of recombinant human protein C in transgenic mice and pigs. Lubon also fails to mention rHuAFP.

As is acknowledged by the Examiner, none of Deboer, Clark, or Lubon, either alone or in combination, teaches or suggests a rHuAFP transgene, a transgenic non-human mammal that expresses and secretes rHuAFP into its milk, methods of producing rHuAFP by using a transgenic non-human mammal to express and secrete rHuAFP into its milk, or milk of a transgenic non-human mammal that contains rHuAFP. To remedy the deficiencies of Deboer, Clark, and Lubon, the Examiner cites Morinaga and Bennett. Morinaga discloses the nucleic acid and predicted amino acid sequence of human AFP, but does not suggest the expression of

rHuAFP in a transgenic non-human mammal under the control of a milk-specific promoter or the secretion of rHuAFP in the milk of that mammal based on the presence of a leader sequence, as is taught in the present specification and recited in present claims 1, 3, 5-7, 10 and 11. Furthermore, Morinaga fails to provide any motivation to express human AFP using recombinant means of any sort. Morinaga merely discloses that three plasmids containing overlapping fragments of the human AFP cDNA sequence (pHAF 2, pHAF 6, and pHAF 7; see, e.g., Fig. 1 of Morinaga) were prepared and sequenced to determine the nucleic acid sequence of human AFP (see, e.g., p. 4604, col. 2). Morinaga fails to teach or suggest the preparation of a single plasmid that contains the full-length coding region of human AFP, a milk-specific promoter, and a leader sequence, much less the expression and secretion of rHuAFP in the milk of a transgenic non-human mammal using such a plasmid.

Bennett discloses the expression of rHuAFP using an *E. coli* expression system (see, e.g., the Abstract). Bennett concludes that the "[a]vailability of large quantities of homogeneous, biologically active recombinant human AFP will facilitate further studies of structure/function, mechanism, and therapeutic potential of this agent as a regulator of breast cancer growth" (Abstract). Bennett, like Morinaga, fails to teach or suggest a nucleic acid molecule containing a nucleic acid sequence encoding rHuAFP, a milk-specific promoter, and a leader sequence. Bennett also fails to teach or suggest the expression and secretion of rHuAFP in the milk of a transgenic non-human mammal; Bennett is limited solely to the expression of rHuAFP in *E. coli*. Thus, nowhere does Morinaga or Bennett provide any suggestion, motivation, or teaching to express rHuAFP in a transgenic non-human mammal or to promote the secretion of rHuAFP in the milk of that mammal.

The Combination of Deboer, Clark, or Lubon with Morinaga and Bennett Fails to Establish Prima Facie Obviousness of Claims 1, 3, 5-7, 10, and 11

The Examiner states:

> The skilled artisan would have a reasonable expectation of success in combining the teachings of Deboer, Clark or Lubon with those of Morinaga because it was routine in the art to express a recombinant gene in the mammary epithelial cells of mammals and a vast array of genes had been utilized and expressed successfully. Thus, the claimed invention, as

> a whole, is clearly prima facie obvious in the absence of evidence to the contrary. Office Action, p. 13.

The Examiner has applied an incorrect standard for assessing obviousness. As is discussed above, the cited references, taken alone or in combination, must provide the necessary motivation, suggestion, or teaching of the desirability of making Applicants' invention. *In re Kotzab*, *supra*. The cited references fail to provide any suggestion, motivation, or teaching to express rHuAFP in a transgenic non-human mammal or to promote the secretion of rHuAFP in the milk of that mammal. To believe that one skilled in the art would be motivated to express and secrete rHuAFP in the milk of a transgenic non-human mammal when none of the cited references discuss, suggest, or mention Applicants' specific combination, either outright or in a way that would lead one to Applicant's invention, is to assume an unstated level of inspiration in the prior art constituting inventive activity. The case law makes clear that to avoid a hindsight-based obviousness analysis the Patent Office bears the burden of elucidating factual teachings, suggestions, or incentives in the prior art that would provide motivation to combine the cited references. *See, e.g., Graham v. John Deere Co.*, 383 U.S. 1, 18, 148 U.S.P.Q. 459, 467 (1966) ("strict observance" of factual predicates to obviousness conclusion required), and M.P.E.P. § 2142, *supra*. Combining Deboer, Clark, or Lubon with Morinaga and Bennett without evidence of a suggestion, teaching, or motivation to do so takes Applicants' disclosure as a blueprint for piecing together the prior art to defeat patentability, which is impermissible. *In re Dembiczak*, *supra*.

Because the combination of Deboer, Clark, or Lubon with Morinaga and Bennett fails to provide any motivation for the skilled artisan to produce a transgenic non-human mammal capable of expressing and secreting rHuAFP in its milk by using a nucleic acid molecule containing a nucleic acid sequence encoding rHuAFP, a milk-specific promoter, and a leader sequence, the combination of cited references does not satisfy the requirements for establishing a *prima facie* case of obviousness. Accordingly, Applicants respectfully request that the rejection of claims 1, 3, 5-7, 10, and 11 under 35 U.S.C. § 103(a) be withdrawn.

CONCLUSION

Applicants submit that present claims 1, 3, 5-7, 10, and 11 are in condition for allowance, and such action is respectfully requested.

Enclosed is a petition to extend the period for replying for three months, to and including September 22, 2005, and a check for the fee required under 37 C.F.R. § 1.17(a).

If there are any other charges, or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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